DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

g1423d

Dallas District
3310 Live Oak Street
Dallas, Texas 75204-6191

June 25, 2001

Ref: 2001-DAL-WL-18

WARNING LETTER

CERTIFIED MAIL
RETURNED RECEIPT REQUESTED

Mr. Weldon S. Guest
President and Executive Director
Transplantation Research Foundation
4545 Bissonnet, Suite 285
Bellaire, Texas 77401

Dear Mr. Guest:

During an inspection of your firm located in Bellaire, Texas on March 9, 12, 13, and 19, 2001, our investigator determined that your firm manufactures human dura mater allografts for tissue implantation. This product is a medical device as defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

Your devices are adulterated within the meaning of Section 501(h) of the Act in that the methods used in, or the facilities or controls used for their manufacturing, packing, storage, or installation are not in conformance with the Current Good Manufacturing Practice (CGMP) requirements of the Quality System Regulations, as specified in Title 21, Code of Federal Regulation (CFR), Part 820. The significant deviations include, but are not limited to, the following:

1. Failure to establish and maintain procedures, including quality requirements, that must be met by contractors [21 CFR 820.50]. For example:

   a. Your firm had no written confirmation of the residual moisture and ethylene oxide (EO) residual results from the [redacted] and has not clearly delineated other quality attributes that must be furnished with each processed dura mater allograft [FDA-483 Item 2(a)].

   b. There is no clear written agreement from the contact manufacturer [redacted] that it will notify your firm of changes in the product or service [FDA-483 Item 2(b)].

2. Failure to establish and maintain procedures for acceptance activities [21 CFR 820.80]. For example:

   a. Your firm received and accepted processed dura mater from [redacted] without written confirmation of the test results, including the moisture and EO residuals [FDA-483 Item 3].

   b. Processed dura maters were released for implantation without the signature and date of the individual authorizing the release [FDA-483 Item 3].

3. Failure to establish and maintain production and process control procedures to ensure conformance to specifications [21 CFR 820.70]. For example:

   a. Your firm has not defined consistent frozen temperature specifications and storage times for harvested dura mater tissues. The inspection reported that your firm was storing the harvested tissues at different frozen temperatures at the [redacted] sites ([redacted] and [redacted]) [FDA-483 Item 4].

   b. During the inspection your freezer's alarm battery low indicator was on. This freezer is used to store dura mater, serum, and archived serum.

   c. Temperature history charts for the freezers located at the [redacted], dated 11/2000 through 2/2001, and the [redacted], dated 1/2000 through 2/2001, contain no signature and name of the individual(s) recording and reviewing the data.

4. Failure to establish and maintain procedures to control product that does not conform to specified requirements [21 CFR 820.90]. For example, the computer disposition records did not clearly document the destruction of unsuitable dura mater, and there are no disposition procedures addressing the segregation and disposition activities for unsuitable dura mater [FDA-483 Item 6(a)].

5. Failure to establish and maintain adequate procedures for the identification, documentation, validation or verification, review, and approval of design changes before their implementation [21 CFR 820.30(i)]. For example, your firm did not validate the [redacted] arbitrary endotoxin (pyrogen) limit of [redacted] [FDA-483 item 5(c)]; or the [redacted] in the postmortem time interval for tissue procurement to [redacted] [FDA-483 Item 5(a)].

6. Failure to establish and maintain procedures for receiving, reviewing, and evaluating complaints [21 CFR 820.198]. For example, the complaint handling procedure "Product Incident Report Procedures", dated 5/2/95, does not specify all the essential requirements of a complaint file [FDA-483 Item 1].

Your dura mater allografts are also misbranded under Section 502(t)(2) of the Act in that information was not submitted to FDA as required by the Medical Device Reporting Regulation, 21 CFR 803.50(a)(1). Specifically, your firm failed to report two incidents of adverse immune reactions to the dura mater device that necessitated surgical procedures to explant the dura mater and replace it with autologous tissue. (see Transplantation Research Foundation Incident Reports dated 3/23/98 and 10/20/00).

The law also requires that manufacturers of medical devices obtain marketing clearance for their products from FDA before they can offer them for sales. This helps protect the public health by ensuring that newly introduced medical devices are safe and effective for their intended uses.

Our records show that you have not submitted a premarket notification [510(k)] for your dura mater allografts. Because you do not have marketing clearance from FDA, marketing your product is a violation of the law. In legal terms, the product is adulterated under Section 501(f)(1)(B) and misbranded under Section 502(o) of the Act. Your product is adulterated under the Act because you did not obtain premarket approval based on information developed by you that shows your device is safe and effective. Your product is misbranded under the Act because you did not submit information that shows your device is substantially equivalent to other devices that are legally marketed.

Transplantation Research Foundation (TRF) would only be exempt from the premarket notification requirements if it acted solely as a distributor of dura mater manufactured by [redacted] or as a repackager that placed its own name on the device but did not change any other labeling or otherwise affect the device. See 21 CFR 807.85(b). According to the [redacted], Dura Mater Processing Agreement between [redacted] and TRF, [redacted] is a contract manufacturer for TRF. Under this agreement, since TRF is responsible for the finished device sold under its name and can set or change the specifications at any time (as it did when it [redacted] limits to [redacted]), it is responsible for submitting a premarket notification. If you have any questions regarding the submission of a premarket notification, you may wish to contact Ms. Heather Rosecrans, Center for Devices and Radiological Health, Office of Device Evaluation at (301) 594-1190.

You were informed in a letter, dated June 15, 2001, from the Center for Devices and Radiological Health's (CDRH) Office of Device Evaluation, that you are required to submit an IDE application to FDA and receive both FDA and institutional review board (IRB) approval before you initiate or continue a study of the clinical significance of [redacted]. Please be advised that it is a violation of the law to initiate or continue such a study without such approvals and without complying with the other requirements of 21 CFR Part 812.

This letter is also to advise you and the [redacted] that a dura mater allograft that contains more than 0.06 EU/ml of endotoxin cannot legally be introduced into interstate commerce unless and until it is the subject of an FDA order finding it to be substantially equivalent to a legally marketed predicate or an approved investigational device exemption.

Your firm is required to register with the FDA both as a "manufacturer" and as a "specification developer," and to list your dura mater allografts. Your firm is a specification developer because [redacted] processes dura mater at your direction for sale under your firm's name. TRF must also register as a manufacturer because of its manufacturing activities. Failure to register your establishment and list your device causes your device to be further misbranded under section 502(o) of the Act.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA-483 issued at the close of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems.

You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

Until these violations are corrected, and FDA has documentation to establish that such corrections have been made, federal agencies will be advised of the issuance of this Warning Letter so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please provide this office in writing within 15 working days of receipt of this letter a report of the specific steps you have taken or will take to identify and correct any underlying systems problems necessary to assure that similar violations will not recur. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time frame within which the corrections will be completed. Your reply should be directed to Mr. Thao Ta, Compliance Officer, at the above letterhead address.

Sincerely,

Michael A. Chappell
Dallas District Director

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cc: [redacted]